Oncogenic transformation of diverse gastrointestinal tissues in primary organoid culture.

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Public Summary:

Scientific Abstract:
The application of primary organoid cultures containing epithelial and mesenchymal elements to cancer modeling holds promise for combining the accurate multilineage differentiation and physiology of in vivo systems with the facile in vitro manipulation of transformed cell lines. Here we used a single air-liquid interface culture method without modification to engineer oncogenic mutations into primary epithelial and mesenchymal organoids from mouse colon, stomach and pancreas. Pancreatic and gastric organoids exhibited dysplasia as a result of expression of Kras carrying the G12D mutation (KrasG12D), p53 loss or both and readily generated adenocarcinoma after in vivo transplantation. In contrast, primary colon organoids required combinatorial Apc, p53, KrasG12D and Smad4 mutations for progressive transformation to invasive adenocarcinoma-like histology in vitro and tumorigenicity in vivo, recapitulating multi-hit models of colorectal cancer (CRC), as compared to the more promiscuous transformation of small intestinal organoids. Colon organoid culture functionally validated the microRNA miR-483 as a dominant driver oncogene at the IGF2 (insulin-like growth factor-2) 11p15.5 CRC amplicon, inducing dysplasia in vitro and tumorigenicity in vivo. These studies demonstrate the general utility of a highly tractable primary organoid system for cancer modeling and driver oncogene validation in diverse gastrointestinal tissues.